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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/028,410	12/19/2001	Yves Dubaquie	P1712R1-1D1	4233

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EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 02/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/028,410	DUBAQUIE ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) *8-14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-14* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

The amendment of 15 October 2003 has been entered in full. Claims 1-2, 4-5, and 7 are amended.

This application contains claims 8-14 drawn to an invention nonelected with traverse in the response of 25 April 2003. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-7 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objections to the specification at pg 2-3 of the previous Office Action (18 July 2003) are *withdrawn* in view of the amended title and specification (15 October 2003).

2. The objection to claim 4 at pg 3 of the previous Office Action (18 July 2003) is *withdrawn* in view of the claim amendment (15 October 2003).

3. The rejections to claims 1-7 under 35 U.S.C. § 112, second paragraph, as set forth at pg 6-7 of the previous Office Action (18 July 2003) are *withdrawn* in view of the amended claims (15 October 2003). Please see new rejection under 35 U.S.C § 112, second paragraph, below.

Claim Rejections - 35 USC § 112, first paragraph

4. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with

which it is most nearly connected, to make and/or use the invention. The basis for this rejection is set forth for claims 1-7 at pg 3-6 of the previous Office Action (18 July 2003).

Claims 1-7 are directed to a method for treating a disorder characterized by dysregulation of the growth hormone/insulin-like growth factor (GH/IGF) axis in a mammal comprising administering to the mammal an effective amount of an IGF-I variant wherein the amino acid residue at position 16, 25, or 49 or the amino acid residues at positions 3 and 49 of native-sequence human IGF-I are replaced with an alanine, a glycine, or serine residue. The claims also recite numerous disorders, including renal disorders. The claims recite further administering to the mammal an effective amount of a renally-active peptide, sulfonyl-containing, sulfonamide-containing, angiotensin-converting enzyme inhibitor, or antibody molecule that promotes reabsorption or retention of electrolytes. The claims recite that the mammal is a human and wherein the amino acid residues at positions 3 and 49 of native sequence human IGF-1 are replaced with alanine residues.

Applicant's arguments (15 October 2003), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) Applicant asserts that disorders characterized by dysregulation of the GH/IGF axis share common defects, clinical manifestations, and biochemical profile (pg 6-7 of Response of 15 October 2003). Applicant argues that the specification provides disclosure sufficient to teach one of ordinary skill in the art how to practice the claimed invention. Applicant contends that Example 3 of the specification discloses how a peptide of the invention may be used to bind to a IGFBP and displace endogenous IGFs in humans. Applicant states that in addition to Example 3 and teachings discussed by the Examiner regarding experiments at pg 41 of the specification, the

specification provides a significant amount of disclosure describing how to practice the invention. Applicant cites, for example, pages 21-26 of the specification.

Applicant contends at pg 9 of the Response that the quantity of experimentation required to determine the parameters for the treatment methods claimed in the application is not large and consists of experiments that are routine in the art. Applicant asserts that the amount of direction or guidance provided in the specification is considerable. Applicant submits that the specification includes working examples (Examples 2-3). Applicant contends that the nature of the invention and the state of the art at the time of the invention are such that the methods for using the animal data and human protocols presented in the specification may be routinely applied to provide the claimed methods. Applicant argues that the relative skill in the pharmaceutical and medical arts is high, requiring less disclosure in order to teach one of ordinary skill in the art. Applicant also states that the predictability or unpredictability of the art is moderate since the state of the art is well advanced regarding clinical manifestations of disorders characterized by dysregulation of the GH/IGF axis in a mammal is well advanced. Applicant asserts that the breadth of the claims is small given that the claims are directed specifically to a method of treating clinical manifestations of a disorder only in mammals.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed at pg 4-5 of the previous Office Action (28 July 2003), the phrase "disorder characterized by dysregulation of the GH/IGF axis" in the claims is interpreted by the Examiner to be broad, in that it encompasses any and all diseases or disorders involved in the regulation of anabolic and metabolic homeostasis (specification pg 11, lines 23-25). The specification of the instant application does not teach treating any disorder characterized by dysregulation of the

GH/IGF axis in a mammal by administration of any IGF-I variant. Undue experimentation would be required of the skilled artisan to determine the optimal quantity, duration, and route of administration of an IGF-I variant wherein the amino acid residue at position 16, 25, or 49 or the amino acid residues at positions 3 and 49 of native-sequence human IGF-I are replaced with an alanine, a glycine, or serine residue. Although Applicant states that Example 3 of the specification (pg 42-43) provides a significant amount of disclosure describing how to practice invention, this example only shows the principle of how an exogenously administered peptide that binds to one or more of the IGFBPs acts to displace endogenous IGFs. For example, the methods of Example 3 teach the administration of recombinant human IGF-I or placebo to patients with type II diabetes (pg 42, lines 26-27). The concentrations of IGF-I, IGF-II, and IGFBP-3 are measured. However, Example 3 does not teach that type II diabetes is *treated* with the administration of IGF-I. Furthermore, Example 3 does not teach the administration of *any IGF-I variant* to a subject with all possible disorders characterized by dysregulation of the GH/IGF axis, as required by the claims. Additionally, although the specification teaches at pg 41 that IGF-I variants are radiolabeled and administered to rats, the specification only measures clearance of the variants from the blood. The specification does not disclose that a disorder is treated by the variants. These experiments are not adequate guidance, but are merely an invitation for the artisan to use the current invention as a starting point for further experimentation. Overall, the specification does not teach the treatment of any disorders by any IGF-I variants, particularly the double mutant (E3A/F49A) and single mutant (F49A) variants. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the

claimed objectives may be an issue to be considered in determining the quantity of experimentation needed".

The specification also outlines prophetic procedures for treatment of disorders characterized by dysregulation of the GH/IGF axis at pg 21-26. However, this is not adequate guidance, but again, is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The claimed method may not necessarily treat the clinical manifestations of a disorder characterized by dysregulation of the GH/IGF axis. The skilled artisan must resort to trial and error experimentation and such trial and error experimentation is considered undue. Although the claimed method may utilize routine administration and agent formulation techniques, the results of the method are unpredictable and complex when combined with the step of administering any IGF-I variant to treat the clinical manifestations of any disorder characterized by dysregulation of the GH/IGF axis. Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily treat the clinical manifestations of a disorder characterized by dysregulation of the GH/IGF axis by administration of an IGF-I variant.

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to treat all possible disorders characterized by dysregulation of the GH/IGF axis by administration of an IGF-I variant and to determine what effect an "effective amount" of an IGF-I variant has, the lack of direction/guidance presented in the specification regarding the same, the absence of working examples directed to the same, the complex nature of the invention, and the unpredictability of the effects of administration of an IGF-I variant for all disorders characterized by dysregulation of the GH/IGF axis (see discussion), undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

35 USC § 112, second paragraph

5. Claims 1-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. The term "clinical manifestations" in claims 1-7 is a relative term which renders the claims indefinite. The term "clinical manifestations" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. Although pg 5 of the Response of 15 October 2003 indicates that support for "clinical manifestations" is located at pg 8 and 11 of the specification, it is inappropriate to read limitations in the specification into the claims. The claims must independently define the invention for which patent protection is sought. Therefore, the claims are rejected as being

indefinite because the claims do not clearly define the symptoms or conditions that are treated by administration of an IGF-I variant.

Conclusion

No claims are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

BEB
Art Unit 1647
09 February 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER